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WO 02/051232 A2

(54) Title: NOVEL BENZAZEPINES AND RELATED HETEROCYCLIC DERIVATIVES

(57) Abstract: The invention relates to novel benzazepines and related heterocyclic derivatives and their use as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as orexin receptor antagonists.

Novel Benzazepines and related heterocyclic derivatives

The present invention relates to novel benzazepines and related heterocyclic derivatives of the general formula (I) and their use as pharmaceuticals. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more compounds of formula (I), and especially their use as orexin receptor antagonists.

The orexins (hypocretins) comprise two neuropeptides produced in the hypothalamus: the orexin A (OX-A) (a 33 aminoacid peptide) and the orexin B (OX-B) (a 28 aminoacid peptide) (Sakurai T. *et al.*, **Cell**, 1998, 92, 573-585). Orexins are found to stimulate food consumption in rats suggesting a physiological role for these peptides as mediators in the central feedback mechanism that regulates feeding behavior (Sakurai T. *et al.*, **Cell**, 1998, 92, 573-585). On the other hand, it was also proposed that orexins regulate states of sleep and wakefulness opening potentially novel therapeutic approaches for narcoleptic patients (Chemelli R.M. *et al.*, **Cell**, 1999, 98, 437-451). Two orexin receptors have been cloned and characterized in mammals. They belong to the superfamily of G-protein coupled receptor (Sakurai T. *et al.*, **Cell**, 1998, 92, 573-585). The orexin-1 receptor (OX_1) is selective for OX-A and the orexin-2 receptor (OX_2) is capable to bind OX-A as well as OX-B.

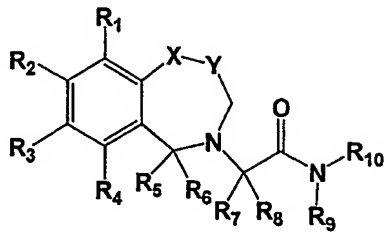
Orexin receptors are found in the mammalian host and may be responsible for many biological functions such as pathologies including, but not limited to, depression; anxiety; addictions; obsessive compulsive disorder; affective neurosis; depressive neurosis; anxiety neurosis; dysthymic disorder; behaviour disorder; mood disorder; sexual dysfunction; psychosexual dysfunction; sex disorder; schizophrenia; manic depression; delirium; dementia; severe mental retardation and dyskinesias such as Huntington's disease and Tourette syndrome; feeding disorders such as anorexia, bulimia, cachexia and obesity; diabetes; appetite/taste disorders; vomiting/nausea; asthma; cancer; Parkinson's disease; Cushing's syndrome/disease; basophil adenoma; prolactinoma; hyperprolactinemia; hypopituitarism; hypophysis tumor/adenoma; hypothalamic diseases; inflammatory bowel disease; gastric diskinesia; gastric ulcus; Froehlich's syndrome; adrenohypophysis disease; hypophysis disease; pituitary growth hormone; adrenohypophysis hypofunction; adrenohypophysis hyperfunction; hypothalamic

hypogonadism; Kallman's syndrome (anosmia, hyposmia); functional or psychogenic amenorrhea; hypopituitarism; hypothalamic hypothyroidism; hypothalamic-adrenal dysfunction; idiopathic hyperprolactinemia; hypothalamic disorders of growth hormone deficiency; idiopathic growth deficiency; dwarfism; gigantism; acromegaly; disturbed biological and circadian rhythms; sleep disturbances associated with diseases such as neurological disorders, neuropathic pain and restless leg syndrome; heart and lung diseases, acute and congestive heart failure; hypotension; hypertension; urinary retention; osteoporosis; angina pectoris; myocardinal infarction; ischaemic or haemorrhagic stroke; subarachnoid haemorrhage; ulcers; allergies; benign prostatic hypertrophy; chronic renal failure; renal disease; impaired glucose tolerance; migraine; hyperalgesia; pain; enhanced or exaggerated sensitivity to pain such as hyperalgesia, causalgia, and allodynia; acute pain; burn pain; atypical facial pain; neuropathic pain; back pain; complex regional pain syndrome I and II; arthritic pain; sports injury pain; pain related to infection e.g. HIV, post-chemotherapy pain; post-stroke pain; post-operative pain; neuralgia; conditions associated with visceral pain such as irritable bowel syndrome, migraine and angina; urinary bladder incontinence e.g. urge incontinence; tolerance to narcotics or withdrawal from narcotics; sleep disorders; sleep apnea; narcolepsy; insomnia; parasomnia; jet-lag syndrome; and neurodegerative disorders including nosological entities such as disinhibition-dementia-parkinsonism-amyotrophy complex; pallido-ponto-nigral degeneration epilepsy; seizure disorders and other diseases related to orexin.

The present invention provides benzazepines and related heterocyclic derivatives which are non-peptide antagonists of human orexin receptors, in particular OX_1 and OX_2 receptors. In particular, these compounds are of potential use in the treatment of obesity and/or sleep disorders.

So far not much is known about low molecular weight compounds which have a potential to antagonise either specifically OX_1 or OX_2 or both receptors at the same time. Recently WO 99/09024, WO 99/58533, WO 00/47577 and WO 00/47580 have been published wherein phenyl urea and phenyl thiourea derivatives are described as being preferably OX_1 receptor antagonists. Also quite recently WO 00/47576 described cinnamide derivatives as OX_1 receptor antagonists. The novel compounds of the present invention belong to an entirely different class of low molecular weight compounds as compared to all prior art orexin receptor antagonists so far published.

The present invention relates to novel benzazepines and related heterocyclic derivatives of the general formula (I).



Formula (I)

wherein:

R^1, R^2, R^3, R^4 independently represent cyano, nitro, halogen, hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy, heterocyclylalkyloxy, $R^{11}CO$-, $NR^{12}R^{13}CO$-, $R^{12}R^{13}N$-, $R^{11}OOC$-, $R^{11}SO_2NH$-, or R^{14}-CO-NH-, or R^2 and R^3 together as well as R^1 and R^2 together and R^3 and R^4 together may form with the phenyl ring a five, six or seven-membered saturated ring containing one or two oxygen atoms;

R^5, R^6, R^7, R^8, R^9, R^{10} independently represent hydrogen, aryl, aralkyl, lower alkyl, lower alkenyl, trifluoromethyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl;

R^{11} represents lower alkyl, lower alkenyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^{12}$and R^{13} independently represent hydrogen, lower alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

R^{14} represents lower alkyl, aryl, cycloalkyl, heterocyclyl, $R^{12}R^{13}N$-, $R^{11}O$-;

-X-Y- independently represents $-CH_2-CH_2-$, $-O-CH_2-$, $-S-CH_2-$, $-SO_2-CH_2-$ and $-NR^{15}-CO-$;

R^{15} represents hydrogen, lower alkyl or aralkyl.

The compounds of formula (I) can contain one or more asymmetric centres and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixtures of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

In the present description the term "lower alkyl", alone or in combination, signifies a straight-chain or branched-chain alkyl group with 1 to 6 carbon atoms, preferably a straight or branched-chain alkyl group with 1-4 carbon atoms. Examples of straight-chain and branched C_1-C_8 alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl, n-heptyl, n-octyl, isobutyl, tert-butyl, the isomeric pentyls, the isomeric hexyls, the isomeric heptyls and the isomeric octyls, preferably methyl, ethyl, n-propyl, isopropyl, n-butyl, 2-butyl, tert-butyl and n-pentyl.

The term "lower alkenyl", alone or in combination, signifies a straight-chain or branched-chain alkenyl group with 2 to 5 carbon atoms, preferably allyl and vinyl.

The term "lower alkoxy", alone or in combination, signifies a group of the formula alkyl-O- in which the term "alkyl" has the previously given significance, such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy and tert-butoxy, preferably methoxy and ethoxy.

Lower alkenyloxy groups are preferably vinyloxy and allyloxy.

The term "cycloalkyl", alone or in combination, signifies a cycloalkyl ring with 3 to 8 carbon atoms and preferably a cycloalkyl ring with 3 to 6 carbon atoms. Examples of C_3-C_8 cycloalkyl are cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl, preferably cyclopropyl, cyclohexyl and particularly cyclohexyl or lower alkyl substituted cycloalkyl which may preferably be substituted

with lower alkyl such as methyl-cyclopropyl, dimethyl-cyclopropyl, methyl-cyclobutyl, methyl-cyclopentyl, methyl-cyclohexyl, dimethyl-cyclohexyl.

The term "aryl", alone or in combination, signifies a phenyl or naphthyl group which optionally carries one or more substituents, preferably one or two substituents, each independently selected from cyano, halogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, nitro, trifluoromethyl, trifluoromethoxy, amino, carboxy and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-tert-butoxyphenyl, 4-fluorophenyl, 2-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl and 2-naphthyl. Preferred are carboxyphenyl, lower alkoxy-phenyl, hydroxyphenyl and particularly phenyl.

The term "aralkyl", alone or in combination, signifies an alkyl or cycloalkyl group as previously defined in which one hydrogen atom has been replaced by an aryl group as previously defined. Preferred are benzyl and benzyl substituted in the phenyl ring with hydroxy, lower alkyl, lower alkoxy or halogen preferably chlorine. Particularly preferred is benzyl.

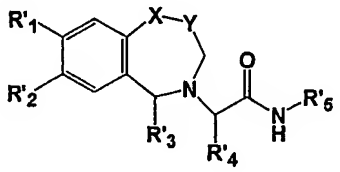
For the term "heterocyclyl" and "heterocyclyl-lower alkyl", the heterocyclyl group is preferably a 5- to 10-membered monocyclic or bicyclic ring, which may be saturated, partially unsaturated or aromatic containing for example 1, 2 or 3 heteroatoms selected from oxygen, nitrogen and sulphur which may be the same or different. Example of such heterocyclyl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, pyridyl, pyrimidinyl, pyrazinyl, pyridazinyl, quinolyl, isoquinolyl, thienyl, thiazolyl, isothiazolyl, furyl, imidazolyl, pyrazolyl, pyrrolyl, indazolyl, indolyl, isoindolyl, isoxazolyl, oxazolyl, quinoxalinyl, phthalazinyl, cinnolinyl, dihydropyrrolyl, pyrrolidinyl, isobenzofuranyl, tetrahydrofuranyl,

dihydropyranyl. The heterocyclyl group may have up to 5, preferably 1, 2 or 3 optional substituents. Examples of suitable substituents include halogen, lower alkyl, amino, nitro, cyano, hydroxy, lower alkoxy, carboxy and lower alkyloxy-carbonyls.

The term "halogen" signifies fluorine, chlorine, bromine or iodine and preferably chlorine and bromine and particularly chlorine.

The term "carboxy", alone or in combination, signifies a –COOH group.

A group of preferred compounds according to the present invention are compounds of formula (II)



General formula (II)

wherein:

R'^1 and R'^2 independently represent hydrogen, hydroxy, lower alkoxy, lower alkenyloxy or halogen or may form with the phenyl ring a five, six or seven membered-ring containing one or two oxygen atoms;

R'^3, R'^4, R'^5 independently represent aryl, aralkyl, lower alkyl, lower alkenyl, hydrogen trifluoromethyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl;

-X-Y- independently represents $-CH_2-CH_2-$, $-O-CH_2-$, $-S-CH_2-$, $-SO_2-CH_2-$ and $-NR'^6-CO-$;

R'^6 represents hydrogen, lower alkyl or aralkyl.

The compounds of formula (II) can contain one or more asymmetric centres and can be present in the form of optically pure enantiomers, mixtures of enantiomers such as, for example, racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms

and pharmaceutically acceptable salts thereof.

Examples of preferred compounds of formula (II) are:

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-naphthalen-1-ylmethyl-acetamide

N-Benzo[1,3]dioxol-5-ylmethyl-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-2-yl-acetamide

2-[5-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl]-*N*-indan-2-yl-acetamide

2-[5-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl]-*N*-indan-1-yl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

2-[9-(3,4-Dimethoxy-benzyl)-2,3-dimethoxy-5,5-dioxo-5,6,7,9-tetrahydro-5λ-thia-8-aza-benzocyclohepten-8-yl]-*N*-indan-2-yl-acetamide

2-[9-(3,4-Dimethoxy-benzyl)-2,3-dimethoxy-5,5-dioxo-5,6,7,9-tetrahydro-5λ-thia-8-aza-benzocyclohepten-8-yl]-*N*-indan-1-yl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-2-yl-2-phenyl-acetamide

2-[9-(3,4-Dimethoxy-benzyl)-2,3-dimethoxy-6,7-dihydro-9H-5-thia-8-aza-benzocyclohepten-8-yl]-*N*-naphthalen-1-ylmethyl-acetamide

2-[9-(3,4-Dimethoxy-benzyl)-2,3-dimethoxy-6,7-dihydro-9H-5-thia-8-aza-benzocyclohepten-8-yl]-*N*-(2-ethoxy-benzyl)-acetamide

2-[9-(3,4-Dimethoxy-benzyl)-2,3-dimethoxy-6,7-dihydro-9H-5-thia-8-aza-benzocyclohepten-8-yl]-*N*-indan-1-yl-acetamide

2-[5-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl]-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide

N-Benzyl-2-[9-(3,4-dimethoxy-benzyl)-2,3-dimethoxy-6,7-dihydro-9H-5-thia-8-aza-benzocyclohepten-8-yl]-acetamide

2-[5-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl]-*N*-indan-1-yl-acetamide

N-Butyl-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-2-phenyl-acetamide

N-Benzo[1,3]dioxol-5-ylmethyl-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

N-Cyclopentyl-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-furan-2-ylmethyl-2-phenyl-acetamide

{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetylamino}-acetic acid ethyl ester

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-*N*-pyridin-4-ylmethyl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-*N*-pyridin-3-ylmethyl-acetamide

N-Cyclopropyl-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-(2-oxo-tetrahydro-furan-3-yl)-2-phenyl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-(4-methoxy-indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-(3-phenyl-indan-1-yl)-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-(4-methyl-indan-1-yl)-acetamide

2-{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetylamino}-3-hydroxy-propionic acid methyl ester

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-ethylcarbamoylmethyl-2-phenyl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-[(ethyl-methyl-carbamoyl)-methyl]-2-phenyl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-8-hydroxy-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

2-[8-Benzyloxy-1-(3,4-dimethoxy-benzyl)-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

3-{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetylamino}-propionic acid methyl ester

N-Benzo[1,3]dioxol-5-ylmethyl-2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

N-(1H-Benzoimidazol-2-ylmethyl)-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

2-[8-Allyloxy-1-(3,4-dimethoxy-benzyl)-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7-methoxy-8-propoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

3-{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetylamino}-*N*,*N*-dimethyl-propionamide

3-{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetylamino}-*N*-ethyl-*N*-methyl-propionamide

2-[1-(3,4-Dimethoxy-benzyl)-8-isopropoxy-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

2-[8-(2,2-Difluoro-ethoxy)-1-(3,4-dimethoxy-benzyl)-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

Examples of particularly preferred compounds of formula (II) are:

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-2-yl-acetamide

2-[5-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl]-*N*-indan-1-yl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-2-yl-2-phenyl-acetamide

N-Butyl-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-2-phenyl-acetamide

N-Benzo[1,3]dioxol-5-ylmethyl-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

N-Cyclopentyl-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-furan-2-ylmethyl-2-phenyl-acetamide

{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetylamino}-acetic acid ethyl ester

2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-*N*-pyridin-3-ylmethyl-acetamide

3-{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetylamino}-propionic acid methyl ester

N-(1H-Benzoimidazol-2-ylmethyl)-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

2-[8-Allyloxy-1-(3,4-dimethoxy-benzyl)-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-7-methoxy-8-propoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

2-[1-(3,4-Dimethoxy-benzyl)-8-isopropoxy-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

2-[8-(2,2-Difluoro-ethoxy)-1-(3,4-dimethoxy-benzyl)-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

Examples of physiologically usable or pharmaceutically acceptable salts of the compounds of formula (I) are salts with physiologically compatible mineral acids such as hydrochloric acid, sulphuric or phosphoric acid; or with organic acids such as methanesulphonic acid, acetic acid, trifluoroacetic acid, citric acid, fumaric acid, maleic acid, tartaric acid, succinic acid or salicylic acid. The compounds of formula (I) with free carboxy groups can also form salts with physiologically compatible bases.

Examples of such salts are alkali metal, alkali earth metal, ammonium and alkylammoniumsalts such as Na, K, Ca or tetraalkylammonium salt. The compounds of formula (I) can also be present in the form of a zwitterion.

Preferred compounds as described above have IC_{50} values below 1000 nM;

especially preferred compounds have IC_{50} values below 100 nM which have been determinated with the FLIPR (Fluorometric Imaging Plates Reader) method described in the beginning of the experimental section.

The compounds of the general formula (I) and their pharmaceutically usable salts can be used for the treatment of diseases or disorders where an antagonist of a human orexin receptor is required such as obesity, diabetes, prolactinoma, narcolepsy, insomnia, sleep apnea, parasomnia, depression, anxiety, addictions, schizophrenia and dementia.

The compounds of formula (I) and their pharmaceutically usable salts are particularly useful for the treatment of obesity and sleep disorders.

The compounds of formula (I) and their pharmaceutically usable salts can be used as medicament (e.g. in the form of pharmaceutical preparations). The pharmaceutical preparations can be administered internally, such as orally (e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions), nasally (e.g. in the form of nasal sprays) or rectally (e.g. in the form of suppositories). However, the administration can also be effected parenterally, such as intramuscularly or intravenously (e.g. in the form of injection solutions).

The compounds of formula (I) and their pharmaceutically usable salts can be processed with pharmaceutically inert, inorganic or organic adjuvants for the production of tablets, coated tablets, dragées, and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc. can be used, for example, as such adjuvants for tablets, dragées, and hard gelatine capsules.

Suitable adjuvants for soft gelatine capsules, are, for example, vegetable oils, waxes, fats, semi-solid substances and liquid polyols, etc.

Suitable adjuvants for the production of solutions and syrups are, for example, water, polyols, saccharose, invert sugar, glucose, etc.

Suitable adjuvants for injection solutions are, for example, water, alcohols, polyols, glycerol, vegetable oils, etc.

Suitable adjuvants for suppositories are, for example, natural or hardened oils, waxes, fats, semi-solid or liquid polyols, etc.

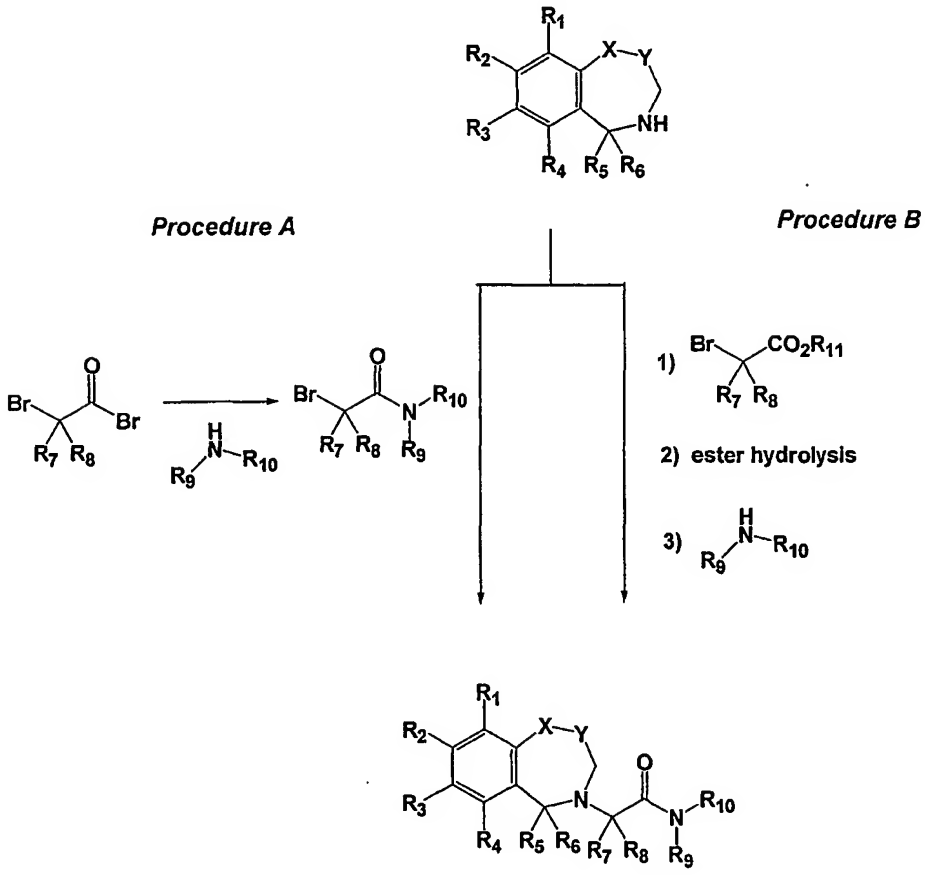
Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, viscosity-increasing substances, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances. The invention also relates to processes for the preparation of compounds of Formula (I).

The compounds of general formula (I) of the present invention are prepared according to the general sequence of reactions outlined in the schemes below, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10} are as defined in formula (I) above. As the case may be any compound obtained with one or more optically active carbon atom may be resolved into pure enantiomers or diastereomers, mixtures of enantiomers or diastereomers, diastereomeric racemates and the meso-forms in a manner known per se.

The compounds obtained may also be converted into a pharmaceutically acceptable salt thereof in a manner known per se.

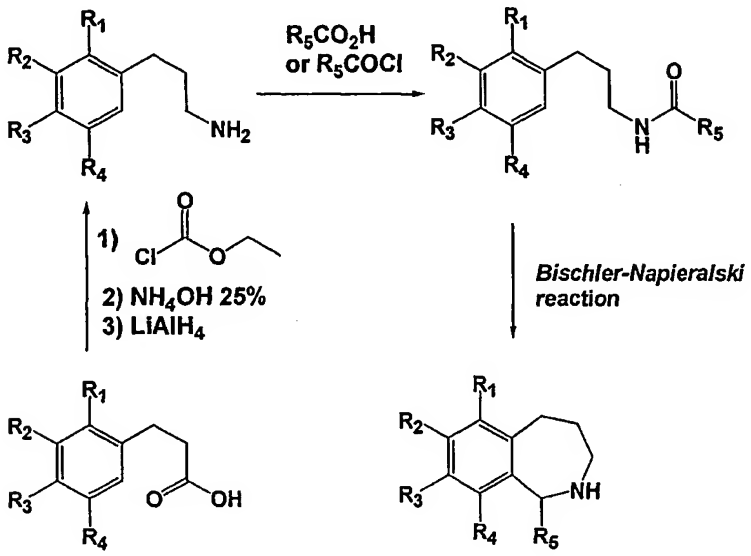
The compounds of the general formula (I) may be prepared by standard procedures

(*procedure A* wherein R^7 and R^8 are hydrogen) and (*procedure B* wherein R^7 and R^8 are other than hydrogen) shown in *Scheme 1* using synthesized benzazepine and related heterocyclic derivatives.



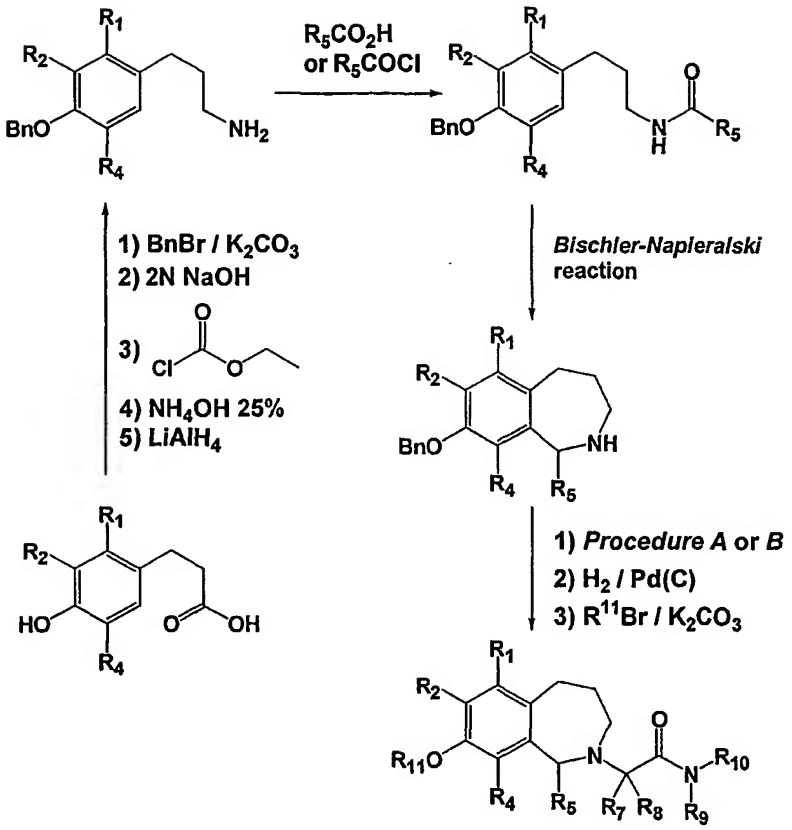
Scheme 1

Benzazepine derivatives wherein X and Y are CH_2 and R^6 is hydrogen might be prepared from the corresponding phenylpropylamine by coupling with the desired carboxylic acid or acyl chloride followed by treatment with $POCl_3$ and finally $NaBH_4$ (Bischler-Napieralski reaction) as shown in *Scheme 2a.*



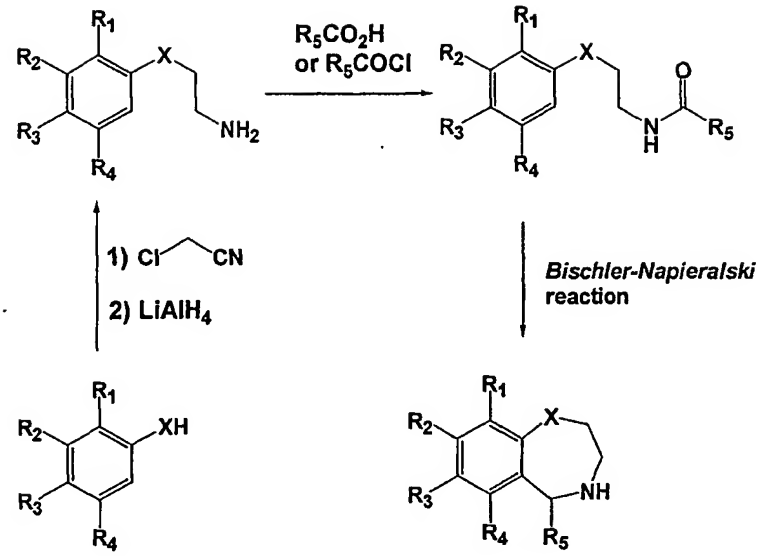
Scheme 2a

Benzazepines with variable substituents on position 8 might be prepared by hydrogenolysis of the corresponding 8-benzyloxy-1,3,4,5-tetrahydro-benzazepines followed by *O*-alkylation with the appropriate electrophile (*Scheme 2b*). The benzylethers can be obtained with the previous procedure (*Scheme2a*) applied to 3-(4-benzyloxy-phenyl)-propionic acid derivatives.



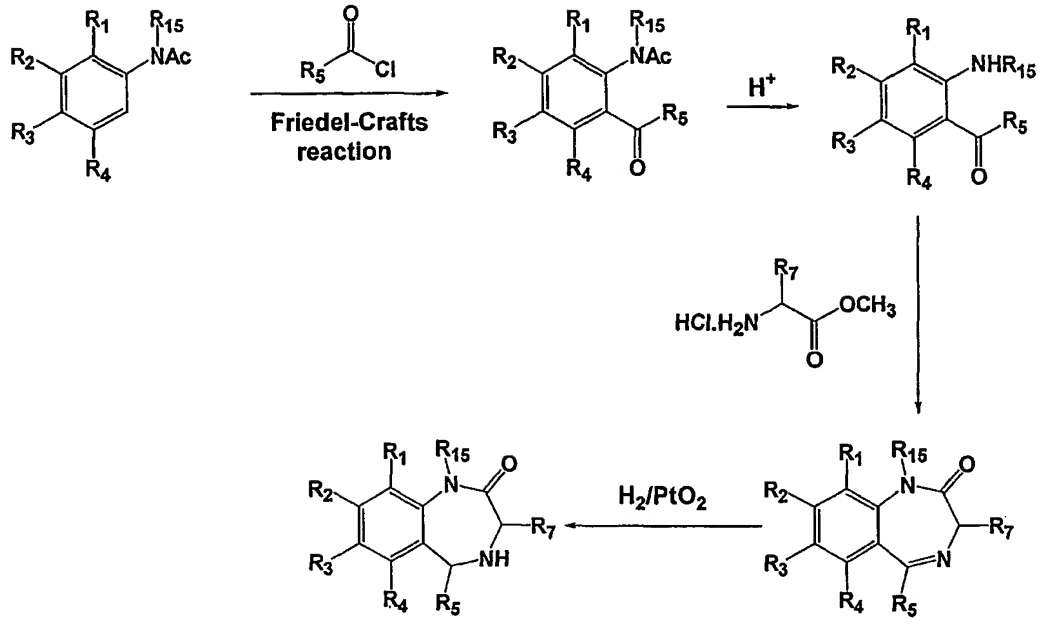
Scheme 2b

Benzothiazepine and benzoxazepine derivatives wherein X is O or S, Y is CH_2 and R^6 is hydrogen might be prepared from the corresponding arylamine by coupling with the desired carboxylic acid or acyl chloride followed by treatment with $POCl_3$ and finally $NaBH_4$ (Bischler-Napieralski reaction) as shown in *Scheme 3*.



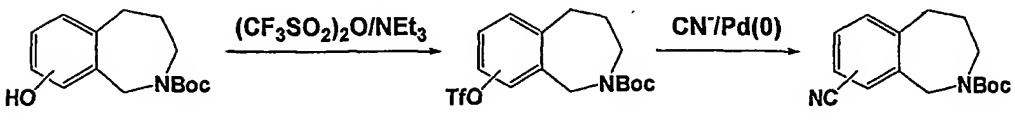
Scheme 3

1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one derivatives wherein X is NR^{15}, Y is CO ; R^6 is hydrogen might be prepared by Friedel-Crafts acylation of the correspond acetamido-aniline with the respective acyl chloride (Sternbach L.H. *et al.*, **J. Org. Che** 1962, 27, 3781-3788), followed by *N*-deprotection, cyclisation by treatment with met esters of α-amino acids (Sternbach L.H. *et al.*, **J. Org. Chem.**, 1962, 27, 3788-3796) ; finally hydrogenolysis of the dihydro compound (Fryer R.I. *et al.*, **J. Med. Chem.**, 19 386-389) (*Scheme 4*).



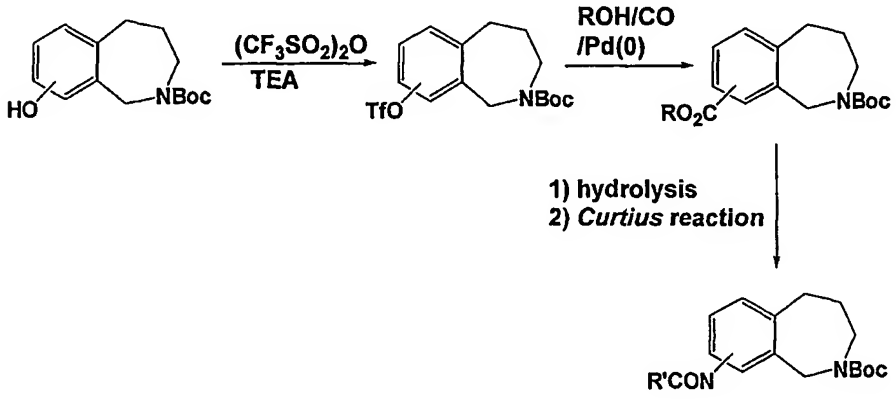
Scheme 4

For the preparation of benzazepine derivatives with electron-withdrawing substituents on the phenyl ring, the previous procedures based on the *Bischler-Napieralski* reaction are incompatible. Therefore cyano groups might be introduced by reaction of a triflate with cyanide ions and palladium(0) (Austin N.E. *et al.*, **Bioorg. Med. Chem. Lett.**, 2000, 10, 2553-2555; Ritter K. *et al.*, **Synthesis**, 1993,735; Selnick H.G. *et al.*, **Synth. Commun.** 1995, 25, 20, 3255-3262) (*Scheme 5*).



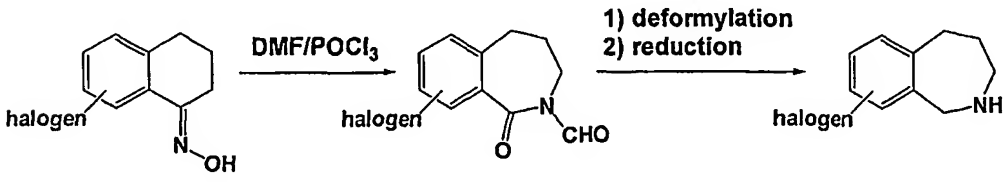
Scheme 5

Carboxylic groups might also be introduced by reaction of a triflate with carbon monoxide, an alcohol and palladium(0) (Roth G.P. *et al.*, **Tetrahedron Lett.**, 1992, 33, 1959; Ma D. *et al.*, **Bioorg. Med. Chem. Lett.**, 1998, 8, 18, 2447-2450; Fisher M.J. *et al.*, **J. Med. Chem.**, 1997, 40, 2085-2101; Kraus G.A. *et al.*, **Tetrahedron Lett.**, 1994, 35, 9189-9190). These carboxylic functions can subsequently be converted into amino functionalties by hydrolysis and *Curtius* reaction (*Scheme 6*).



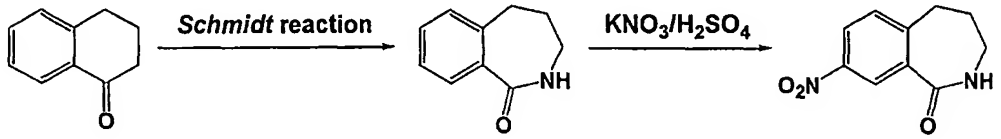
Scheme 6

Halogen containing 2-benzazepines may be prepared by treatment of halogenated tetralone oximes with $POCl_3$/DMF and the resulting 1,3,4,5-tetrahydro-1-oxo-2*H*-2-benzazepine-2-carboxaldehydes can be subsequently deformylated and reduced (Majo V.J. *et al.*, **Synth. Commun.**, 1995, 25, 23, 3863-3868) (*Scheme 7*).



Scheme 7

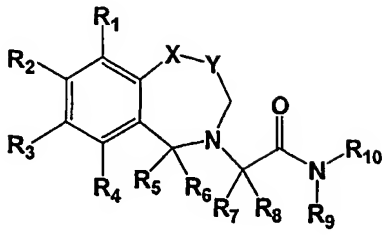
8-nitro-2,3,4,5-tetrahydro-1*H*-2-benzazepine might be prepared by regioselective nitratic of 2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one using potassium nitrate and sulfuric ac (Grunewald G.L. *et al.*, **J. Heterocyclic Chem.**, 1994, 31, 1609-1617) (*Scheme 8*).



Scheme 8

Claims

1. Compounds of the general formula (I)



Formula (I)

wherein:

R^1, R^2, R^3, R^4 independently represent cyano, nitro, halogen, hydrogen, hydroxy, lower alkyl, lower alkenyl, lower alkoxy, lower alkenyloxy, trifluoromethyl, trifluoromethoxy, cycloalkyloxy, aryloxy, aralkyloxy, heterocyclyloxy, heterocyclylalkyloxy, $R^{11}CO$-, $NR^{12}R^{13}CO$-, $R^{12}R^{13}N$-, $R^{11}OOC$-, $R^{11}SO_2NH$- or R^{14}-CO-NH- or R^2 and R^3 together as well as R^1 and R^2 together and R^3 and R^4 together may form with the phenyl ring a five, six or seven-membered ring containing one or two oxygen atoms;

R^5, R^6, R^7, R^8, R^9, R^{10} independently represent hydrogen, aryl, aralkyl, lower alkyl, lower alkenyl, trifluoromethyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl;

R^{11} represents lower alkyl, lower alkenyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

$R^{12}$and R^{13} independently represent hydrogen, lower alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl or heterocyclyl-lower alkyl;

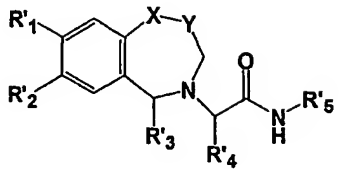
R^{14} represents lower alkyl, aryl, cycloalkyl, heterocyclyl, $R^{12}R^{13}N$- or $R^{11}O$-;

-X-Y- independently represents $-CH_2-CH_2-$, $-O-CH_2-$, $-S-CH_2-$, $-SO_2-CH_2-$ and $-NR^{15}$-CO-;

R^{15} represents hydrogen, lower alkyl or aralkyl.

and optically pure enantiomers, mixtures of enantiomers racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

2. Compounds of the general formula (II)



Formula (II)

wherein:

R'^1 and R'^2 independently represent hydrogen, hydroxy, lower alkoxy, lower alkenyloxy or halogen or may form with the phenyl ring a five, six or seven membered-ring containing one or two oxygen atoms;

R'^3, R'^4, R'^5 independently represent aryl, aralkyl, lower alkyl, lower alkenyl, trifluoromethyl, cycloalkyl, heterocyclyl or heterocyclyl-lower alkyl;

-X-Y- independently represents $-CH_2-CH_2-$, $-O-CH_2-$, $-S-CH_2-$, $-SO_2-CH_2-$ and $-NR'^6-CO-$;

R'^6 represents hydrogen, lower alkyl or aralkyl.

and optically pure enantiomers, mixtures of enantiomers racemates, optically pure diastereoisomers, mixtures of diastereoisomers, diastereoisomeric racemates, mixture of diastereoisomeric racemates, or meso forms and pharmaceutically acceptable salts thereof.

3. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-naphthalen-1-ylmethyl-acetamide

4. *N*-Benzo[1,3]dioxol-5-ylmethyl-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-acetamide

5. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-2-yl-acetamide

6. 2-[5-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl]-*N*-indan-2-yl-acetamide

7. 2-[5-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl]-*N*-indan-1-yl-acetamide

8. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

9. 2-[9-(3,4-Dimethoxy-benzyl)-2,3-dimethoxy-5,5-dioxo-5,6,7,9-tetrahydro-5l6-thia-8-aza-benzocyclohepten-8-yl]-*N*-indan-2-yl-acetamide

10. 2-[9-(3,4-Dimethoxy-benzyl)-2,3-dimethoxy-5,5-dioxo-5,6,7,9-tetrahydro-5l6-thia-8-aza-benzocyclohepten-8-yl]-*N*-indan-1-yl-acetamide

11. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

12. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-2-yl-2-phenyl-acetamide

13. 2-[9-(3,4-Dimethoxy-benzyl)-2,3-dimethoxy-6,7-dihydro-9H-5-thia-8-aza-benzocyclohepten-8-yl]-*N*-naphthalen-1-ylmethyl-acetamide

14. 2-[9-(3,4-Dimethoxy-benzyl)-2,3-dimethoxy-6,7-dihydro-9H-5-thia-8-aza-benzocyclohepten-8-yl]-*N*-(2-ethoxy-benzyl)-acetamide

15. 2-[9-(3,4-Dimethoxy-benzyl)-2,3-dimethoxy-6,7-dihydro-9H-5-thia-8-aza-benzocyclohepten-8-yl]-*N*-indan-1-yl-acetamide

16. 2-[5-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-2,3-dihydro-5H-benzo[f][1,4]oxazepin-4-yl]-*N*-(1,2,3,4-tetrahydro-naphthalen-1-yl)-acetamide

17. *N*-Benzyl-2-[9-(3,4-dimethoxy-benzyl)-2,3-dimethoxy-6,7-dihydro-9H-5-thia-8-aza-benzocyclohepten-8-yl]-acetamide

18. 2-[5-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-2,3-dihydro-5H-benzo[f][1,4]oxazepi 4-yl]-*N*-indan-1-yl-acetamide

19. *N*-Butyl-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

20. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-2-phenyl-acetamide

21. *N*-Benzo[1,3]dioxol-5-ylmethyl-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

22. *N*-Cyclopentyl-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

23. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-furan-2-ylmethyl-2-phenyl-acetamide

24. {2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetylamino}-acetic acid ethyl ester

25. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-*N*-pyridin-4-ylmethyl-acetamide

26. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-*N*-pyridin-3-ylmethyl-acetamide

27. *N*-Cyclopropyl-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

28. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-(2-oxo-tetrahydro-furan-3-yl)-2-phenyl-acetamide

29. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-(4-methoxy-indan-1-yl)-acetamide

30. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-(3-phenyl-indan-1-yl)-acetamide

31. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-(4-methyl-indan-1-yl)-acetamide

32. 2-{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetylamino}-3-hydroxy-propionic acid methyl ester

33. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-ethylcarbamoylmethyl-2-phenyl-acetamide

34. 2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-[(ethyl-methyl-carbamoyl)-methyl]-2-phenyl-acetamide

35. 2-[1-(3,4-Dimethoxy-benzyl)-8-hydroxy-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

36. 2-[8-Benzyloxy-1-(3,4-dimethoxy-benzyl)-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

37. 3-{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetylamino}-propionic acid methyl ester

38. *N*-Benzo[1,3]dioxol-5-ylmethyl-2-[1-(3,4-dimethoxy-benzyl)-8-hydroxy-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

39. *N*-(1H-Benzoimidazol-2-ylmethyl)-2-[1-(3,4-dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetamide

40. 2-[8-Allyloxy-1-(3,4-dimethoxy-benzyl)-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

41. 2-[1-(3,4-Dimethoxy-benzyl)-7-methoxy-8-propoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

42. 3-{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetylamino}-*N,N*-dimethyl-propionamide

43. 3-{2-[1-(3,4-Dimethoxy-benzyl)-7,8-dimethoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-2-phenyl-acetylamino}-*N*-ethyl-*N*-methyl-propionamide

44. 2-[1-(3,4-Dimethoxy-benzyl)-8-isopropoxy-7-methoxy-1,3,4,5-tetrahydro-benzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

45. 2-[8-(2,2-Difluoro-ethoxy)-1-(3,4-dimethoxy-benzyl)-7-methoxy-1,3,4,5-tetrahydrobenzo[c]azepin-2-yl]-*N*-indan-1-yl-acetamide

46. Pharmaceutical compositions for the treatment of disorders which are associated with the role of orexin, especially disorders such as obesity and sleep disorders, comprising containing a compound of any one of claims 1 to 45, or a pharmaceutically acceptable salt thereof, and usual carrier materials and adjuvants.

47. The compounds of any one of claims 1 to 45, or a pharmaceutically acceptable salt thereof, for use as medicaments for the treatment of disorders which are associated with a role of orexin, especially obesity and sleep disorders.

48. A method of treating or preventing diseases or disorders where an antagonist of a human orexin receptor is required, which comprises administering to a subject in need thereof an effective amount of a compound as claimed in any one of claims 1 to 45, or a pharmaceutically acceptable salt thereof.

49. A process for the manufacture of pharmaceutical compositions for the treatment of disorders associated with the role of orexin, especially obesity and sleep disorders, containing one or more compounds as claimed in any one of claims 1 to 15, or a pharmaceutically acceptable salt or salts thereof, as active ingredients which process comprises mixing one or more active ingredient or ingredients with pharmaceutically acceptable excipients and adjuvants in a manner known per se.

50. A compound as described as end-product in any one of examples 1 to 43.

51. The invention as hereinbefore described.